REMARKS

Claim 1, 3, 4, 11, 18, 21 and 23 are currently being examined. Claims 1, 3, 4, 11, 18, and 21 have been amended. Claims 12 and 13 are withdrawn from consideration. New claim 23 has been added. Claims 2, 5-10,14-17, 19, 20 and 22 have been canceled without prejudice. The fact that claims 2, 5-10, 14-17, 19, 20 and 22 have been canceled is not to be construed an admission by Applicant or Applicant's attorney that such claims are not patentable, and Applicant reserves the right to pursue the subject matter of the canceled claims in a divisional or continuing application. In addition, Applicant asserts that no new matter has been added.

Objections to the Specification

Applicant has amended Figure 3 and the paragraphs on page 4 beginning on line 17 and page 28 beginning in line 1 in response to Examiner's objection to Figure 3. Also, Applicant has amended the paragraph on page 27 beginning on line 12 to accurately reflect the correct address of the ATCC.

Rejection under 35 U.S.C. § 101

A. The Examiner has rejected claims 1-4, and 18 under 35 U.S.C. § 101 as being directed to non-statutory matter. In particular, the Examiner asserts that the claims do not sufficiently distinguish over a polypeptide or an immunogenic fragment thereof as it exists naturally. *See*, Office Action, paragraph 8, page 4.

In response Applicant has amended claims 1 and 18 to recite "...an isolated polypeptide..." Support for this amendment can be found on page 8, lines 6-14 and lines 16-24 of the application as filed. Thus, no new matter has been added.

In view of the above amendments Applicant respectfully requests that patentability of claims 1 and 18 under 35 U.S.C. §101 be reconsidered and the rejection withdrawn.

Rejections under 35 U.S.C. § 112

A. The Examiner rejected claims 1-3 and 11 under 35 U.S.C. § 112, first paragraph. In particular, the Examiner states that "the specification fails to teach a single 'variant' having 65-80% sequence identity to the amino acid sequence of SEQ ID NO: 8 or an immunogenic fragment thereof, which concurrently has the ability to bind to a Pneumococcus-specific antibody." *See*, Office Action, Paragraph 9, page 4.

This rejection is respectfully traversed. Applicant believes that there is adequate written description support for the claims as written.

Preliminarily, Applicant has amended claims 1 and 11, cancelled claim 2, and added claim 23. In particular, claim 1 has been amended to recite at least 80% identity. Applicant notes that the value of 80% identity is not critical to the present invention and this amendment should not be considered as a surrendering of equivalent embodiments that have less than 80% identity but greater than 65% identity.

Applicant respectfully points out that section 2163 of the MPEP states that "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support of each species in the genus. *See*, MPEP 2163 (emphasis added). Also, in *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1569 (1997), the Federal Circuit court stated that "[a] description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by a nucleotide sequence, falling within the scope of the genus, *or of a recitation of structural features common to the members of*

the genus." [Emphasis added]. Therefore, the adequate description of a genus of polypeptides can be accomplished by a description of a structural feature common to the members of the genus. Applicant further points out that the Examiner stated that "[a] convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the polypeptide encoded, and the function of the encoded polypeptide". *See*, Office Action Paragraph 9, page 5.

Applicant asserts that the genus of claims 1, 3 and 11 does, in fact, contain a common feature of the genus that is described in the specification. In particular, the claims recite "...and, when administered to a mammal, can elicit an antibody that will bind to *Streptococcus pneumoniae.*" This functional language serves to unite the variants of SEQ ID NO: 8 such that they have a common feature; i.e., a variant sequence of SEQ ID NO: 8 that can elicit an antibody, when administered to a mammal, that will bind to *Streptococcus pneumoniae*. Support for the feature can be found in the specification on page 11 lines 10-24; and page 12 line 14 to page 13, line 30. Moreover, this functional feature of the specified polypeptides is based on the common structural feature of being at least 80% identical to SEQ ID NO: 8 and having the common structural property based on this identity of being able to elicit an antibody that binds *S. pneumoniae*. Thus, Applicant asserts that claims 1, 3, and 11 are adequately described in the specification.

Further, Applicant points out that in *Union Oil Company of California v. Atlantic Richfield Company,* 208 F.3d 989, 998 (2000), the Federal Circuit stated that "[t]he written description requirement does not require the Applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.'" (Quoting In *re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1997)). Applicant asserts that one of ordinary skill in the art would recognize that an invention that encompasses the polypeptide of SEQ ID NO: 8 will also encompass certain variants of SEQ ID NO: 8. In addition, one of ordinary skill in the art would recognize that a polypeptide variant of SEQ ID NO: 8,

when injected into a mammal, can elicit an antibody that will bind to *Streptococcus*. Thus, Applicant asserts that one skilled in the art would recognize or envision the subject matter of claims 1, 3 and 11.

The Examiner further asserts that "[t]he function cannot be predicted from the modification of the structure of the gene and in the instant case, the DNA encoding the recited peptide variant." *See*, Office Action paragraph 9, page 5. Applicant has amended claim 1 to recite such a function. The claims merely require that an immunogenic composition elicit an antibody specific for *Streptococcus pneumoniae*. In addition, determining antigenicity of a polypeptide is not unpredictable. Methods to determine antigenicity have been known to persons skilled in the art for over a decade. *See*, e.g., Jameson, B.A. and H. Wolf (1988) " The antigenic index: a novel algorithm for predicting antigenic determinants," CABIOS, 4: 181-186 (abstract provided on Exhibit A). Moreover, there are computer programs, e.g. DNAstar, that could readily determine a protein's antigenicity. Thus, Applicant believes that persons of ordinary skill after reading the specification would indeed recognize the invention as claimed.

In addition, the Examiner asserts that "Applicants have not shown that variation or modification of a reference sequence encoding a reference protein as claimed would automatically predict the production of a protein variant having the recited functional activity, i.e., ability to bind to an antibody specific to *Streptococcus pneumoniae*." *See*, Office Action paragraph 9, page 5. In response, Applicant respectfully reminds the Examiner that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed, *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976)and the examiner bears the initial burden of presenting reasons why a person skilled in the art would not recognize that the written description of the invention provided support for the claims. *See*, MPEP 2163. Accordingly, Applicant does not believe that the Examiner has provided evidence to support a rejection under 35 U.S.C. § 112, first paragraph, for lack of written description. In fact, Applicant has presented evidence that the written description is met by virtue of the examples and figures

forming a part of the specification. Thus, Figure 3 shows that one protein can be used to raise antisera against a variety of strains while Figure 4 shows reactivity of patient antisera with either Sp128 or Sp130, which proteins differ in sequence. (see description of Figures 3 and 4 on page 4)

If the Examiner believes that polypeptides meeting the limitations of the relevant claims would not elicit production of antibodies for Streptococcus then the Examiner is invited to provide evidence of such. For example, the streptococcal organisms themselves vary in antigenic determinants (see description of Figure 3) yet they elicit production of antibodies after infecting an animal. Evidently, there is room for variability in the amino acid sequence of a potential immunogenic polypeptide useful in vaccines and immunogenic compositions. By amending claim 1 to recite that the polypeptide elicits production of antibodies specific for Streptococcus pneumoniae when administered to a mammal and by providing, in the examples a ready procedure for testing such polypeptides for immunogenicity together with limited percent identity with respect to SEQ ID NO: 8, Applicant has well enabled those in the art to make and use the invention as recited in amended claim 1.

Therefore, in view of the above and the claim amendments, Applicant believes there is adequate written description support for claims 1, 3 and 11. It is therefore requested that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

B. The Examiner rejected claims 1-4, 11, 21 and 22 under 35 U.S.C. § 112. In particular, the Examiner asserts that, while being enabling for an immunogenic composition or a vaccine containing a purified serotype 4 *Streptococcus pneumoniae* comprising the amino acid of SEQ ID NO: 8, the specification does not reasonably provide enablement for a polypeptide comprising an amino acid sequence having at least 65% to 95% identity to SEQ ID NO: 8 (i.e., a polypeptide variant).

This rejection is respectfully traversed. Applicant asserts that the specification adequately enables a person skilled in the art to practice the invention as claimed.

Preliminarily, Applicant has amended claims 1 and 21, cancelled claim 2 and 22, and added claim 23.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d. 778, at 785.

Claims 1, 3 and 4, as amended, recite an immunogenic composition comprising an isolated polypeptide, or immunogenic fragments thereof, wherein said polypeptide is in a pharmaceutically acceptable carrier and can elicit an antibody specific for *Streptococcus pneumoniae*. Applicant respectfully points out the experiments to test whether a variant binds to an antibody that binds to *Streptococcus pneumoniae* are not undue and are, in fact, routine in the art once the novel antigen of the present invention has been taught. Also, Applicant asserts that the specification teaches a person of ordinary skill in the art to practice the invention. In particular, examples 1 and 2 in the specification discloses methods that could be used to determine if SEQ ID NO: 8 variants bind to an antibody that binds to *Streptococcus pneumoniae*. For instance, examples 1 and 2 describe routine ELISAs that can be used to determine whether an antibody that binds to *Streptococcus pneumoniae* also binds to variants of SEQ ID NO: 8. Furthermore, these experiments are not complex and a person skilled in the art can readily run the experiments. Applicant respectfully reminds the Examiner that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (CCPA, 1976). Even the number of tests to be performed may not give rise to a need for undue experimentation when such tests are relatively routine and straightforward as they are here. Thus, it is well known to those skilled in this art how to quickly generate a range of

polypeptides having a specified sequence identity to that recited by Applicant and to test these for specificity in binding to S. pneumoniae as well as eliciting antibodies specific therefor when administered, for example, to mice. Such procedures are, today, quickly and readily performed on a large scale. Applicant reminds the Examiner that the level of skill in this art is very high and the experiments to test SEQ ID NO: 8 and its variants are routine. Thus, a person of ordinary skill in the art, after reading the specification, can determine if SEQ ID NO: 8 variants can elicited an antibody response that will also bind to *Streptococcus pneumoniae.*

Claims 11 and 21 claim a vaccine against *Streptococcus pneumoniae.* Applicant respectfully points out the experiments to test whether a variant can elicit a protective immune response are also not undue and are, in fact, routine in the art once provided the teachings of the present specification. Firstly, the specification, in particular examples 1 and 2 , disclose certain methods that could be used to determine if the variants can be used as a vaccine. For instance, the examples describe routine immunizations and challenges to mammals. Secondly, these experiments are not complex and a person skilled in the art can readily run the experiments and determine if variants of SEQ ID NO: 8 can be used as a vaccine. The Applicant, again, respectfully reminds the Examiner that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *Id.* In addition, as pointed out above, the level of the skill in the art is very high and the experiments to test SEQ ID NO: 8 and its variants are routine in the art. Thus, a person of ordinary skill in the art, after reading the specification, can determine if variants of SEQ ID NO: 8 can elicit a protective antibody response against *Streptococcus pneumoniae.*

Furthermore, the Examiner asserts that there is no "evidence" in the specification to establish that variants of SEQ ID NO: 8 will bind an antibody that binds to *Streptococcus pneumoniae* and that will serve as a vaccine. *See,* Office Action Paragraph 10, page 6. Applicant respectfully points out that the Examiner has the initial burden of establishing a reasonable basis to question enablement provided for the

claimed invention. *See,* MPEP 2164.04. In addition, "the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." *In re Chilowsky*, 229 F.2d 457, 461 (CCPA, 1956). Thus, the burden lies with the Examiner to show why SEQ ID NO: 8 variants would not elicit an antibody response against *Streptococcus pneumoniae*. Having no "evidence" is not sufficient to establish a 35 U.S.C. § 112 rejection.

Furthermore, the Examiner states that the "specification provided no guidance as to which amino acids must be retained in the polypeptide variant or fragment and which may be varied or deleted without causing any detrimental effect to the claimed product that is meant for inducing an immune response in a mammal." *See*, Office Action, Paragraph 10, page 6.

Applicant respectfully disagrees with this statement. It has been well known for over a decade which amino acids can and cannot be substituted without causing certain effects on the antigenicity a protein. The mere fact that the Examiner found a few journal articles that show the one substitution causes a detrimental affect to a protein does not constitute evidence that the whole field is unpredictable. The focus on the instant claims should be on whether the antigenicity of the variant proteins has changed and whether this can be tested using routine methods. Determining antigenicity of a protein and or polypeptide has been known to persons skilled in the art for a long time. *See*, *e.g.* Jameson, B.A. and H. Wolf (1988) "The antigenic index: a novel algorithm for predicting antigenic determinants," CABIOS, 4: 181-186. In addition, there are computer programs, *e.g.* DNAstar, that could readily determine a protein's antigenicity. Therefore, Applicant asserts that the art is not unpredictable. Also, any variant could be easily tested using the methods disclosed in examples one and two of the specification rendering such predictability unnecessary. At the time the application was filed, all the methods needed to practice the invention were well known. These experiments are routine and are not considered undue experimentation. Therefore Applicant believes

that a person with ordinary skill in the art after reading the application can make and use the invention.

Therefore in view of the above, and the claim amendments, Applicant believes the specification does enable a person skilled in the art to practice the invention. It is therefore requested that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

C. The Examiner has rejected claim 11 under 35 U.S.C. § 112, first paragraph. In particular, the Examiner asserts that, while being enabling for an immunogenic composition or a vaccine containing a purified serotype 4 *Streptococcus pneumoniae* comprising the amino acid sequence of SEQ ID NO: 8, the specification does not reasonably provide enablement for the term "animal". *See*, Office Action, Paragraph 11, page 9.

In response, Applicant has amended claim 11 to recite "mammal".

In addition, the Examiner has rejected claim 11 under 35 U.S.C. § 112, first paragraph, because the Examiner asserts that, while being enabling for an immunogenic composition or a vaccine containing a purified serotype 4 *Streptococcus pneumoniae* comprising the amino acid sequence of SEQ ID NO: 8, the specification does not reasonably provide enablement for all *Streptococcus* species. *See*, Office Action, Paragraph 11, page 9.

In response Applicant has amended claim 11 to recite "...to elicit protective antibodies in a mammal against <u>*S. pneumoniae*</u>."

Therefore in view of the claim amendments, Applicant requests that the rejection of claim 11 under 35 U.S.C. § 112 first paragraph be reconsidered and withdrawn.

D. The Examiner has rejected claims 1-4, 11, 18, 21 and 22 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention. In particular:

a. Examiner asserts that claim 11 is vague and indefinite and confusing in the recitation "of the genus of *Streptococcus*".

In response, claim 11 has been amended to remove the language objected to.

b. Examiner states that claim 1 is confusing in the recitation "composition comprising a polypeptide, including immunogenic fragments thereof".

In response, Applicant has amended claim 1 to remove the language objected to.

c. The Examiner has the same criticism as b above to claim 18.

In response, Applicant has amended claim 18 to recite "composition comprising an isolated polypeptide, or immunogenic fragment thereof..."

d. The Examiner asserts that Claim 11 has improper antecedence for the recitation of "said polypeptide" because the earlier recitation in the claim is "polypeptides".

Applicant has amended claim 11 to recite to remove the language objected to.

e. The Examiner asserts that Claim 22 has is an improper antecedence for the recitation "said immunogenic fragment", where the antecedent, in claim 18, is "immunogenic fragments".

Applicant has cancelled claim 22. Thus, this rejection is now moot.

f. The Examiner asserts that Claim 21 is indefinite and confusing in the limitation: "said immunogenic fragments comprise one or more of the fragments." In particular, the Examiner asserts that the term fragments necessarily has to include more that "one" fragment and cannot have "one" fragment recited.

In response, Applicant has amended claim 21 to recite "said immunogenic fragment comprises one or more..."

g. The Examiner asserts that Claim 11 is confusing or lacks proper antecedent basis for the recitation: "*S. pneumoniae* polypeptides selected from the group consisting of the polypeptides of claims 1, 2, 3, and 4". In addition the Examiner points out that claim 11 depends from claims 1, 2, 3, or 4 which does not refer to the polypeptides as "*S. pneumoniae* polypeptides".

In response, Applicant has amended claim 11 to remove the language objected to.

h. The Examiner asserts that claims 21 and 22 are vague and indefinite in that these claims fail to distinctly identify SEQ ID NO: 8 as the amino acid sequence.

In response to the rejection, Applicant has amended claim 21 to recite "of the amino acid sequence of SEQ ID NO: 8". Claim 22 has been cancelled, thus the rejection as applied to claim 22 is moot.

i. Claims 2-4, 11, 21, and 22, which depend directly or indirectly from claim 1 or 18 are rejected as being indefinite for reasons mentioned above. Applicant has amended the claims appropriately (see a-h above).

In view of the above amendments, Applicant respectfully requests that rejection of claims 1-4, 11, 18, 21 and 22 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 102 (b)

A. The Examiner rejected claims 21 and 22 under 35 U.S.C. § 102 (b) as being anticipated by Choi *et al.* (WO 98/18930). Specifically the Examiner states that Choi *et al.* discloses the polypeptide of amino acid 657 – 773 of the amino acid sequence of SEQ ID NO: 8.

Applicant has cancelled claim 22 and amended claim 21 by removing the fragment 657-773. Thus, in view of the amendments, Applicant respectfully requests that rejection under of claims 21 and 22 under 35 U.S.C. § 102 (b) be withdrawn.

Conclusion

Applicant believes that this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is thereby solicited.

Applicants have included herewith a Request for a 2 month extension of time to respond and a check for the fee for a large entity. No additional fee is believed due in filing this response. If any additional fee is due, the Commissioner is authorized to charge any and all such fees to Deposit Account No. 03-0678.

FIRST CLASS CERTIFICATE

I hereby certify that this correspondence is being deposited today with the U.S. Postal Service as First Class Mail in an envelope addressed to:

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Alan J. Grant 7/23/04
Alan J. Grant, Esq. **Date**

Respectfully submitted,

Alan J. Grant

Alan J. Grant, Esq.
Reg. No. 33,389

CARELLA, BYRNE BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
5 Becker Farm Road
Roseland, NJ 07068
Phone: 973-994-1700
Fax: 973-994-1744

Bioinformatics, Vol 4, 181-186, Copyright © 1988 by Oxford University Press

ARTICLES

The antigenic index: a novel algorithm for predicting antigenic determinants

BA Jameson and H Wolf
Division of Biology, California Institute of Technology, Pasadena, CA 91125.

In this paper, we introduce a computer algorithm which can be used to predict the topological features of a protein directly from its primary amino acid sequence. The computer program generates values for surface accessibility parameters and combines these values with those obtained for regional backbone flexibility and predicted secondary structure. The output of this algorithm, the antigenic index, is used to create a linear surface contour profile of the protein. Because most, if not all, antigenic sites are located within surface exposed regions of a protein, the program offers a reliable means of predicting potential antigenic determinants. We have tested the ability of this program to generate accurate surface contour profiles and predict antigenic sites from the linear amino acid sequences of well-characterized proteins and found a strong correlation between the predictions of the antigenic index and known structural and biological data.

This article has been cited by other articles:

The Journal of Neuroscience ▸HOME

E. M. Sigurdsson, E. Knudsen, A. Asuni, C. Fitzer-Attas, D. Sage, D. Quartermain, F. Goni, B. Frangione, and T. Wisniewski
An Attenuated Immune Response Is Sufficient to Enhance Cognition in an Alzheimer's Disease Mouse Model Immunized with Amyloid-{beta} Derivatives
J. Neurosci., July 14, 2004; 24(28): 6277 - 6282.
[Abstract] [Full Text] [PDF]

Infection and Immunity ▸HOME

J. S. Spencer, H. J. Kim, A. M. Marques, M. Gonzalez-Juarerro, M. C. B. S. Lima, V. D. Vissa, R. W. Truman, M. L. Gennaro, S.-N. Cho, S. T. Cole, and P. J. Brennan
Comparative Analysis of B- and T-Cell Epitopes of Mycobacterium leprae and Mycobacterium tuberculosis Culture Filtrate Protein 10
Infect. Immun., June 1, 2004; 72(6): 3161 - 3170.